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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,213	01/03/2002	Anthony T. Maurelli	04995.0044-01	7868

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	8

DATE MAILED: 10/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,213	MAURELLI ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8 and 41-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,7,8 and 41-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 5/13/03, Paper No. 7B is made. Claims 1-4, 7-8 and 43-47 are currently pending.

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered newly presented claims 9-14 have been renumbered as claims 42-47 and their dependencies have been corrected in a corresponding manner.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "the gastrointestinal order" in . There is insufficient antecedent basis for this limitation in the preceding claim. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 7, 8 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 'a method of attenuating of the effect of *E.coli* and Shigella spp. enterotoxins comprising obtaining a pharmaceutical composition comprising cadaverine and a pharmaceutically acceptable carrier and administering to a host an amount of said pharmaceutical composition effective to attenuate the effect of *E.coli* and Shigella spp. enterotoxins (and wherein said pharmaceutical composition is an amount effective to attenuate transepithelial migration of polymorphonuclear leukocytes) , does not reasonably provide enablement for 'methods of attenuating of the effect of ***any*** pathogenic bacterial enterotoxin (and/or methods of attenuating transepithelial migration of polymorphonuclear leukocytes) comprising administering **(*any*)** diaminoalkyl compound and a pharmaceutically acceptable carrier' or for pharmaceutical compositions comprising any diaminoalkyl compound with these intended uses. Additionally, the specification has not enabled the use of putrescine for attenuating ***any*** pathogenic bacterial enterotoxin and/or attenuating transepithelial migration of polymorphonuclear leukocytes. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

First, diaminoalkyl compounds encompass a huge class of different compounds. The specification provides no experiments with diaminoalkyl groups other than cadaverine. The class of diaminoalkyl compounds, many of which have no bacterial origin, is so huge and the specification only provides guidance and results for the use of one specific diaminoalkyl compound, i.e, cadaverine, it would take one of skill in the art undue experimentation to practice the claimed invention. The scope of the instant claims is not enabled by what is presented in the instant specification. Accordingly, the claims are not enabled for the use of any pharmaceutical composition comprising any diaminoalkyl compounds, other than cadaverine, or methods of using said compound to attenuate any bacterial enterotoxin. Further, with respect to cadaverine, the specification has not enabled the use of this compound to attenuate *any* bacterial enterotoxin. The instant specification provides no results of experiments which demonstrate cadaverine's ability to attenuate any bacterial enterotoxins other than that of the Shigella spp. which given it's similarity to the *E.coli* enterotoxin directly correlates to its ability to attenuate an *E.coli* enterotoxin. The specification teaches that cadaverine when applied *in vitro* for thirty minutes to intestinal epithelium or PMNs could attenuate the toxic effect of *Shigella*.. Since the claims have been amended to recite "attenuation" and not prevention or prophylaxis, these results are sufficient to enable new claim 45 which specifies that the diaminoalkyl compound is cadaverine. However, these results do not demonstrate the attenuation of any other bacterial enterotoxins in a

human or in an animal. Bacterial enterotoxins from different Genus vary greatly. The prior art teaches that what is effective against one bacterial enterotoxin does not correlate directly to bacterial enterotoxin toxins from other Genus. The prior teaches that it is highly unpredictable for one substance to attenuate toxins stemming from all of these different origins. Claims 4 and 10 recites bacteria from several different Genus, many of which possess enterotoxins which differ significantly in mode of action and structure from that of *Shigella* and *E.coli*. Further, many of these bacterium are well known in the art to have no known preventative cure, i.e., *M.tuberculosis*. The information provided in the instant specification is not sufficient to enable the broad scope of the instant claims

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

In the instant case, (1) the nature of the invention is the attenuation of *any* bacterial enterotoxin through the use of *any* diaminoalkyl compound. (2) The state of the prior art is silent as to the use of a diaminoalkyl compound in the attenuation of bacterial enterotoxins. Additionally, the state of the prior art with regard to treating/attenuating infection caused by

enterotoxins is (3) highly unpredictable. Further, the prior teaches that it is highly unpredictable for one substance to provide relief from or attenuate bacterial enterotoxins stemming so many different origins. The information provided in the instant specification is not sufficient to enable the scope of the instant claims. (4) There is no direction or guidance presented for attenuating bacterial enterotoxins using any diaminoalkyl compound, with the exception of attenuating a Shigella or E.coli enterotoxin through the administration of cadaverine. (5) There are also no working examples relating to the attenuation of any bacterial enterotoxin through the administration of any diaminoalkyl compound present in the instant specification. (6) Accordingly, the quantity of experimentation necessary is undue (7) even though the relative skill of those in the art is high. (8) The specification does not enable the breadth of the instant claims. The specification fails to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (US 5,502,055).

Wang teaches a pharmaceutical composition comprising an effective amount of putrescine and a pharmaceutically acceptable carrier. The phrases "wherein the pharmaceutical composition attenuates the effect of pathogenic bacterial enterotoxins" and "also attenuates transepithelial migration of polymorphonuclear leukocytes" are intended uses only. The composition taught by Wang is in an amount which could inherently attenuate a bacterial enterotoxin. The instant claims are silent as to a specific numerical amount. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Response to Applicants' Arguments:

Applicants argue that Wang does not teach putrescine in an amount to attenuate the activity of bacterial enterotoxins only endotoxins. As stated above, The phrases "wherein the pharmaceutical composition attenuates the effect of pathogenic bacterial enterotoxins" and "also attenuates transepithelial migration of polymorphonuclear leukocytes" are intended uses only. The composition taught by Wang is in an amount which could inherently attenuate a bacterial enterotoxin. The instant claims are silent as to a specific numerical amount and the specification fails to teach a specific amount which would be effective *in vivo*. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

8. Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Dela Vega et al (The Euro Journal. 1995 vol. 14(23): 6059-65).

DelaVega et al teach that cadaverine induces the closing of *E.coli* porins (see abstract). The reference teaches that inhibitors of channel porins are of great value in the design of therapeutic agents (p. 6059, col. 1, bottom of first paragraph). The reference teaches that their finding of porin inhibition by cadaverine opens the way to investigating a series of compounds with inhibitory properties (p. 6059, col. 1, bottom of first paragraph). Claims 1, 2 and 4 are product claims. The phrases "pharmaceutical composition", wherein the pharmaceutical composition attenuates the effect of pathogenic bacterial enterotoxins" and "also attenuates transepithelial migration of polymorphonuclear leukocytes" are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, the it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference. The composition of the prior art and the claimed compositions are structurally identical and therefore the teachings of Dela Vega et al are anticipatory on the composition claims.

Response to Applicants' Arguments:

Applicants argue that dela Vega et al does not teach putrescine in an amount to attenuate the activity of bacterial enterotoxins only endotoxins. As stated above, The phrases "wherein the

pharmaceutical composition attenuates the effect of pathogenic bacterial enterotoxins" and "also attenuates transepithelial migration of polymorphonuclear leukocytes" are intended uses only. The composition taught by Dela Vega is in an amount which could inherently attenuate a bacterial enterotoxin. The instant claims are silent as to a specific numerical amount and the specification fails to teach a specific amount which would be effective *in vivo*. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference. The composition of the prior art and the claimed compositions are structurally identical and therefore the teachings of Dela Vega et al are anticipatory on the composition claims.

9. Claims 1, 2 , 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Dela Vega et al (J.Baceriol., July 1996, 178(13): 3715-3721).

DelaVega et al teach that cadaverine and putrescine induce the closing of bacterial porins (see abstract). It is disclosed that both OmpC and OmpF porins ere inhibited (abstract). The references teaches that four diaminoalkyl compounds, putrescine, cadaverine, spermidine, and spermine, were able to inhibit fluxes of B-lactam antibiotics in live cells and chemotaxin (abstract). The reference teaches that polyamines may act as endogenous modulators of outer membrane permeability (abstract). Claims 1-4 are product claims. The phrases "wherein the

pharmaceutical composition attenuates the effect of pathogenic bacterial enterotoxins" and "also attenuates transepithelial migration of polymorphonuclear leukocytes" are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, the it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference. The composition of the prior art and the claimed compositions are structurally identical and therefore the teachings of Dela Vega et al are anticipatory on the composition claims. The compositions taught by Dela Vega is in an amount which could inherently attenuate a bacterial enterotoxin.

Response to Applicants' Arguments:

Applicants argue that dela Vega et al does not teach putrescine in an amount to attenuate the activity of bacterial enterotoxins only endotoxins. As stated above, The phrases "wherein the pharmaceutical composition attenuates the effect of pathogenic bacterial enterotoxins" and "also attenuates transepithelial migration of polymorphonuclear leukocytes" are intended uses only. The composition taught by Dela Vega is in an amount which could inherently attenuate a bacterial enterotoxin. The instant claims are silent as to a specific numerical amount and the specification fails to teach a specific amount which would be effective *in vivo*. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from

the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference. The composition of the prior art and the claimed compositions are structurally identical and therefore the teachings of Dela Vega et al are anticipatory on the composition claims.

Information Disclosure Statement

9. The IDS' submitted on 5/13/03 and 1/3/02 have yet to be considered at this time. Applicants indicated that copies of the references listed on these IDS' were submitted in the parent application 09/281,274. This file has been unavailable to the Examiner so the references have not yet been reviewed. Signed copies of the IDS' will be mailed to Applicant when the references become available.

Status of claims

10. No claims are allowed. Putrescine and cadaverine were both well known and isolated compounds at the time the invention was made as evidenced by the prior art set forth above. Accordingly, these products combined with solely a pharmaceutically acceptable carrier, which reads on water, are not novel. However, new methods of using these molecules, provided there is enablement and written description for these methods as outlined above, may be allowable.

It is noted that he specification fails to teach *in vivo* results; however, it is has been determined that the *in vitro* results and models are sufficient to enable the amended claims which now require only "attenuation" not 'prevention or prophylaxis'. Since the specification fails to

teach a specific amount for *in vivo* use, it is an insufficient to argue that the compositions taught by the prior art do not teach an effective amount for *in vivo* use and therefore do not anticipate the claims.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 872-9306. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JENNIFER E. GRASER
PRIMARY EXAMINER
10/23/03